

The NTP Host Susceptibility Branch Research and Testing Program – Project Reports

The NTP Host Susceptibility Branch is focused on developing multidisciplinary research projects to investigate individual differences in response to environmental exposure to toxic agents and the associated development of complex polygenic diseases. The main aim of this research is to identify causally related genes and their variant isoforms in mouse models as surrogates for human exposure and to develop predictive tools for genetic-based hazard identification and risk characterization. Based upon the dense genotyping of 15 strains of inbred mice referenced to the sequenced C57BL/6J mouse, more than 8 million SNPs and copy number variants have been described and more await discovery. Projects in progress have been categorized thematically to aid review.

- ADME and Toxicogenetics: Using benzene, which has been extensively studied in animals and humans, we have tested multiple, genetically diverse, mouse inbred strains to determine the variable range of ADME kinetic parameters ([Project 1](#)). We are also using this data to perform haplotype association analysis with ADME kinetic parameters ([Project 2](#)) and to determine the optimal ADME study design for quantitative genetic analysis. In addition, we have used this data to design a low dose benzene inhalation study for quantitative measurement of hematotoxicity and genotoxicity ([Project 3](#)) in order to determine the association between benzene ADME kinetics and inhalation toxicity.
- Environmental Cardiotoxins: Using bis(2-chloroethoxy)methane (CEM), which has a metabolite in common with other known cardiotoxins, we are developing a multiple strain mouse model for the identification of environmental cardiotoxins and susceptibility to cardiotoxicity ([Project 4](#)). Both cancer and heart disease are leading causes of death in the United States, and this project will allow us to gain valuable insight into environmental exposure and heritable determinants to cardiotoxicity.
- Aging, Environmental Exposures, and Disease: For developing cancer models using multiple, genetically diverse, mouse inbred strains, we have expanded our research and testing projects to include developing a benchmark reference database on aging and disease in 10 genetically diverse mouse inbred strains ([Project 5](#)). This database will be used to prepare for multiple-strain toxicology and carcinogenesis studies and to develop and conduct a short-term cancer bioassay using multiple p53 haploinsufficient F1 inbred strains ([Project 6](#)). With this experience and knowledge, we will be prepared to select inbred strains to perform pre-chronic and chronic multi-strain toxicity and disease studies with NTP nominated chemicals. For example, both an alkylanilines class study ([Project 7](#)) and studies to determine the impact of sex and strain on the performance of genomic signatures for predicting hepatocarcinogenesis have been developed ([Project 8](#)).

Individual projects are described briefly to define the scope of this effort to date. At the meeting, we will present preliminary results for studies in progress that use NTP knowledge and experience with a wide variety of chemical agents and their toxicities.